CLINICAL INVESTIGATION: AN OVERVIEW

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1. Background

The Clinical Investigation Program (CIP) authorizes AMEDD personnel to conduct scientific inquiry into basic science in medicine and clinical problems that are of significant concern to the health care of all members of the military community. Clinical research and investigation is designed to address fundamental scientific questions in medicine and to solve day-to-day problems in medicine, to answer questions that arise during patient treatment, and to improve medical care. The Clinical Investigation Program is a key element in Graduate Medical Education (GME) in the Department of the Army, providing residents and fellows with experience in scientific thinking and an opportunity to contribute to the body of knowledge of medicine in general. CIP also contributes in a significant manner to the retention of experienced AMEDD personnel by providing opportunity for scientific inquiry. Army personnel that participate in the program perform research that results in manuscripts for submission to professional journals. Poster presentations of AMEDD sponsored research projects are frequently given at meetings of professional medical societies as well. CIP provides a rich environment for the enhancement of the professional skills and standing of the AMEDD community and is viewed as an integral part of the Army's medical mission.

Clinical investigation can take many forms. Examples include laboratory studies of genetic materials from unidentified donors, development of new medical devices or improvements in the uses of existing medical devices, development of new treatment procedures, surveys on patient satisfaction or similar topics, and new drug trials including participation in nationwide oncology group research.

2. Clinical Research Protocols

A. A clinical investigation project is usually started with the submission of a scientific plan stating the research question or questions (hypothesis), the proposed experiments and methodology, the data to be gathered, the statistical methods to be used to draw conclusions from the data. This plan, called a

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protocol, will usually be submitted through the researcher's medical service or department for scientific review before formal submission for approval. Clinical research projects will fall into one of three categories: exempted research[2]; expedited review[3]; and those requiring full human use review.

B. Exempted Research Protocols: Research involving exempted research categories are not submitted to the scientific and human use review committees for approval. However, exempted protocols require *institutional* approval, to establish that the proposal falls within an exempted research category (an investigator cannot declare his own project to be exempt). The categories for exempted research are: (1) health care delivery and epidemiology studies and surveys; (2) educational methods research; (3) research involving the use of educational tests where subjects cannot be directly or indirectly identified; (4) research involving survey, interview procedures or the observation of public behavior (subject to certain limitations); (5) research involving the collection or study of existing data, documents, records or pathological or diagnostic specimens if publicly available or if subjects cannot be identified directly or through identifiers linked to the subject; (6) research involving individual or group training of military personnel; (7) research involving job related tasks of military or civilian personnel who are qualified to test by duty assignments that call specifically for such qualifications. This list is an **inclusive** list, not examples, of exempted categories.

C. Expedited Review Protocols: Research involving human subjects **may** be given expedited review if it falls into one of the categories listed in Appendix H, AR 40-38 and there is no more than minimal risk[4] to the human subjects involved. The categories are: (1) collection of hair, and nails in a nondisfiguring manner, deciduous teeth[5] and permanent teeth if patient care indicates a need for extraction; (2) collection of excreta and external secretions (such as sweat); (3) collection of physical data using noninvasive procedures routinely employed in clinical medicine (but not x-rays); (4) collection of blood samples by venipuncture, limited to 450 milliliters in an 8-week period and no more often than two times per week; (5) collection of dental plaque and calculus using routine methods; (6) voice recording for research purposes; (7) moderate exercise by healthy volunteers; (8) study of existing data, documents, records, pathological specimens or diagnostic specimens; (9) research on individual or group behavior or characteristics of individuals where the subject's behavior is

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[2]See AR 40-38, Appendix B.
[3]See AR 40-38, Appendix H.
[4]See AR 40-38, Glossary.
[5]Deciduous teeth are teeth of the first dentition.

not manipulated and the research will not involve stress to subjects. As with exempted research protocols, the appendix list is all-inclusive, and both conditions (research in one or more of the categories **and** minimal risk) must apply. Research within this category receives approval under expedited review procedures.[6]

D. Human Use Protocols: All other research involving human subjects is required to receive review by the full Human Use Committee (HUC). The HUC is required to determine the level of risk associated with the protocol; make a recommendation to the approving authority that the protocol be approved (with or without modifications), disapproved, deferred to higher authority, or be exempted from further human use review; and determine the adequacy of the proposed consent process. Scientific review may be conducted either by the Clinical Investigation Committee[7] (CIC), where one has been established, before the protocol is submitted to the HUC, or by the HUC, to assure that the protocol design will yield scientifically valid data.

3. Roles of the Judge Advocate or Attorney-Advisor in the Clinical Research Program.

A. The primary, but not exclusive, role of an attorney in the CIP is to ensure that approved protocols involving human research subjects meet the requirements of obtaining informed consent in conformity with applicable State and local law.[8]

B. Committee Membership: An attorney may be appointed as a member of the Clinical Investigation Committee, or the Human Use Committee or both. In either case the legal advisor is a voting member of the committee. Since Human Use Committees are required to have at least one member whose concerns are primarily nonscientific[9], the appointment of an attorney will both fill this requirement and permit the legal review required by AR 40-38.

C. Review of Gifts, Grants and Other Support of CIP: Legal review of proposed gifts of funds or property to support research will be required. The preferred mechanism, the Cooperative Research and Development Agreement (CRDA), establishes joint research efforts between Federal and non-Federal parties, and may provide for the transfer of funds, and the provision of personnel, services, facilities, equipment or other resources from the non-Federal party for the support of specified research. Where money or anything of any value is proffered as a gift, it must be processed

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[6]AR 40-38, paragraph 3-5*g.*
[7]AR 40-38, paragraph 3-5*b*(3).
[7]AR 40-38, Appendix F, paragraph F-9.

[9]AR 40-38, Appendix F, paragraph F-2*e*

under the provisions of AR 1-100 as supplemented by MEDCOM Supplement 1. However, drugs, placebos, biologics and medical devices that are not commercially available are not considered gifts and may be accepted and accounted for in accordance with local directives.[10]

4. Clinical Investigation Program Committees.

A. Clinical Investigation Committee (CIC): Protocols may be submitted to a Clinical Investigation Committee (if separately established) appointed by the activity commander and composed of individuals qualified by training and experience to review protocols for scientific merit (see footnote 8). When authorized by the Human Use Committee, CIC may also perform required review on expedited review protocols, and review minor changes to previously approved protocols during the period for which approval is authorized. However, the CIC may not *disapprove* a protocol.[11]

B. Radiation Control Committee (RCC): Protocols which expose human subjects to ionizing radiation not intended for diagnosis or treatment require a determination of the risk to benefit to ensure human subjects can be properly informed. All such protocols must have a RCC risk assessment prior to submission to the Human Use Committee.[12]

C. Institutional Animal Care and Use Committee (IACUC): The IACUC reviews all research protocols that use animals as test subjects. Review is required of all protocols to insure scientific merit (in both the research question and experimental design), that the minimum number of animals is used, that the animal model is appropriate for the experiment, and that pain is minimized. The committee is also required to semi-annually review all aspects of animal care, and to complete and file an annual report on animal use with the Department of Agriculture.[13] Special considerations apply if certain animals are to be used in a protocol. A headquarters-level administrative review of studies involving non-human primates, cats, dogs, or marine animals is required. Proposals using chimpanzees must have an additional review by the Interagency Animal Model Committee.[14]

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[10]DoD Directive 6000.8, paragraph E.3.a; AR 40-38, paragraph 3-6*b*(3)*(g)*. AR 40-38 also states that loaned equipment may be treated in the same fashion. However, the revision of AR 40-38 will require that loans of equipment for support of CI be treated as gifts. The Clinical Investigation Regulatory Office (CIRO) currently requires that the loan of equipment be treated as a gift of services as a matter of policy.

[11]AR 40-38, paragraph 3-5*g* and Glossary, Section II; HSC Regulation 40-23, paragraph 6a.

[12]AR 40-38, paragraph 3-5*b*(4).

[13]AR 70-18, paragraph 8, as supplemented by HSC Supplement 1.

[14]DODD 3612.1. A complete discussion of medical research using animals is beyond the scope of this chapter. This Department of Defense directive

D. Human Use Committee (HUC): In addition to the protocol review responsibilities found in paragraph 2-D above, the Human Use Committee reviews protocols involving minors as experimental subjects, determining if assent is required along with consent from the parent or guardian for participation; provides continuing review of protocols approved by the HUC at a frequency appropriate for the level of risk, but not less than annually; and reviews protocols involving experimental medical devices to determine whether the device represents a significant or non-significant risk.[15] The fact that a human use protocol may have been reviewed by a CIC for scientific adequacy does not prevent the HUC from reviewing and requiring changes in the design of a protocol. In MTFs where a CIC has not been separately established, the HUC conducts the full scientific and human use review. Final responsibility for recommending to the approving official approval, approval with changes, deferral of review to a higher authority, disapproval or exemption from further human use review lies with the HUC.[16]

E. Institutional Review Board (IRB): The functional equivalent within the Department of Defense of the IRB is the Human Use Committee. The primary difference between the IRB as established by 45 *Code of Federal Regulations* 46 and the HUC as implemented within the Department of Defense by 32 *Code of Federal Regulations* 219 is in authority to approve, require modification, or disapprove research protocols. The IRB exercises this authority, while the HUC makes recommendations to the approving official.[17] Within the Department of Defense actions required of the IRB are accomplished by a HUC and approving official, when necessary.

5. Authority for Approval of Protocols.

A. Generally the Human Use Committee and Approving Authority, working together, approve clinical investigation protocols at an MTF. The Approving Authority acts on the recommendation (approval, approval with changes, deferral of review to a higher authority, disapproval or exemption from further human use review) of the HUC. The Approving Authority may accept or reject the recommendations, but "will not approve a CI that is disapproved by the HUC."[18] There

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provides a starting place should issues arise on animal research.
[15]AR 40-38, paragraph 3-5*d*, and AR 40-38, Appendix F.
[16]HSC Regulation 40-23, paragraph 6a requires the appointment of an Institutional Review Committee (IRC) for the purpose of reviewing all protocols for scientific adequacy, setting priorities for support, reviewing for medical safety and suitability all protocols involving humans subjects "in accordance with AR 40-38." However, the term "Institutional Review Committee" is not used in that regulation. The membership requirements of the IRC seem to mirror the HUC's, but the functions are similar to the CIC.
[17]AR 40-38, Glossary, Section II.
[18] AR 40-38, paragraph 3-5*e* (1), (2).

are, however, exceptions, as noted in paragraphs B to D below. Examples of the types of protocols that are approved locally are:

1. Animal use, except animal use protocols involving non-human primates, cats, dogs and marine animals are subject to centralized review (see C5 below), laboratory, and chart review protocols.[19]

2. Non-investigational drug studies involving human subjects[20] except those requiring approval at higher levels as listed below.

3. National Cancer Institute (an agency within the National Institutes of Health) sponsored protocols and Group C cancer chemotherapy investigational drug protocols (except those involving marijuana /THC) if HSC Regulation 40-23 requirements are met.

B. Commander, Medical Command (cited as Commander, U.S. Army Health Services Command in some publications) acts as approval authority for:

1. Studies involving investigational drugs or devices except those involving Schedule 1 controlled substances.[21]

2. In addition, reviews all Medical Command protocols, including those approved at the local level. Previously approved protocols may be delayed, disapproved, deactivated, or suspended pending further action at HQ Medical Command.[22]

C. The Surgeon General acts as approval authority for:

1. Protocols from MTFs or DTFs from major Army commands that do not have a HUC or other internal review process.[23]

2. Protocols involving human subjects using Schedule 1 controlled drug substances.[24]

3. Protocols involving the use of DA-sponsored investigational drugs or devices.[25]

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[19]HSC Regulation 40-23, Change 2, paragraph 8c; an approval recommendation from the necessary review committees is also required.
[20]*Id.*
[21]AR 40-38, paragraph 2-7*d;* AR 40-7, paragraph 2-2*a* qualifies this approval authority to "non-DA sponsored or investigator-sponsored investigational drugs or devices used within HSC"
[22]HSC Regulation 40-23, Change 2, paragraph 8d.1.
[23]AR 40-38, paragraph 2-4*d.*
[24]AR 40-7, paragraph 2-1*d*; AR 40-38, paragraph 2-4*f.*
[25]AR 40-7, paragraph 2-1*c.*

4. All in-house and contract research (with exceptions noted in paragraphs 2-1, 2-3, 2-5, and 2-7, AR 40-38) involving human subjects for which the Army has been designated as the executive agent. This authority may be delegated within the chain of command to the lowest level with a HUC except for protocols for which TSG is specifically designated as the approval authority.[26]

D. Other Approval Authorities:

1. Commander, Soldier Support Center, National Capital Region: Under AR 600-46, approves attitude and opinion surveys if the survey involves soliciting personnel outside the command that approves the conduct of the study.

2. Deputy Chief of Staff for Personnel: approves or disapproves all studies involving alcohol and drug abuse programs.[27]

3. Under Secretary of Defense for Acquisition: approves all studies involving the exposure of human subjects to nuclear weapons effect, or to chemical or biological warfare agents.[28]

6. Clinical Investigation Regulatory Office (CIRO).

A. CIRO serves as the Surgeon General's agent for the review and approval of most CI (with the exception of those protocols that must be approved above the Surgeon General's level). Additionally, CIRO develops policy and may act as a point of contact for other Federal agencies involved in medical research, such as the National Institutes of Health, or in the regulation of research, such as the Food and Drug Administration.

B. CIRO has also been designated by The Surgeon General as MEDCOM's "federal laboratory" for the purposes of entering into cooperative research and development agreements under the provisions of the Stevenson-Wydler Technology Innovation Act of 1980 as amended by the Federal Technology Transfer Act.

7. Human Subjects Considerations.

A. Only persons who are fully informed and volunteer in advance to take part in a research protocol may be used as subjects in a clinical investigation. No military member may be ordered to participate in a research project, and punishment for refusal is

[26]AR 40-38, paragraph 2-4*i.*
[27]AR 40-38, paragraph 2-3.
[28]AR 40-38, paragraph 2-1.

explicitly forbidden.[29] Special attention must be paid to methods of recruitment for studies involving military personnel (in training units, for example) to ensure that all personnel are true volunteers.

B. All clinical investigations will be conducted in a manner to minimize the risk of harm to subjects, to insure that unavoidable risks are reasonable in relation to anticipated benefits, and to avoid unnecessary physical or mental suffering. If there is reason to believe that death or a serious injury will result from a research project, it will not be conducted.[30]

C. The minimum number of volunteers necessary to reach a statistically valid conclusion will be used.[31]

D. Volunteers are authorized to receive all necessary medical care for injury or disease that is the proximate result of their taking part in an approve research protocol.[32]

E. A medical monitor (a physician with any necessary specialty qualifications) must be appointed for any protocol that is greater than minimal risk, and one may be appointed at the discretion of the HUC or approving authority for any minimal risk study.[33]

F. Subsistence costs will be waived for subjects who are admitted to the hospital only because of participation in a research protocol, and will be waived for a volunteer already in the hospital but only for the period of additional hospitalization required by participation.[34]

8. Consent.[35]

A. Informed consent generally relates to the agreement to participate in research before the project begins. Informed consent must also be obtained during the research project from active participants if new information is obtained which might affect willingness to continue as a research subject.

B. Consent will be obtained in writing. The purpose of the informed consent document is to provide sufficient information to allow a reasonable decision to be made to participate and to document that consent was obtained. The consent should inform the

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[29]AR 40-38, paragraph 3-3*a*, and 3-3*j.*
[30]AR 40-38, 3-3*f*, and 3-3*h.*
[31]AR 40-38, paragraph 3-3*g.*
[32]AR 40-38, paragraph 3-3*j*, and Appendix E.
[33]AR 40-38, paragraph 3-3*o.*
[34]AR 40-38, paragraph 3-3*j*(2).
[35]AR 40-38, paragraph 3-5*c*; HSC Regulation 40-23, paragraph 6c and Appendix A.

volunteer of the nature of the research project, the duration of participation, the procedures, devices or drugs to be used in the research, the risks involved, and benefits (if any) of participation. The language of the consent form must non-technical so that it can be clearly understood by a subject who has no familiarity with medical terminology.

9. Volunteers.

A. Active Duty Military Personnel: may participate, but may only be compensated for blood withdrawal. The maximum compensation is $50.00 per blood withdrawal.[36]

B. Civilian Employees: may participate during duty time for which the employee is paid at straight time rates. Employees must have the approval of their immediate supervisor to participate. Participation outside normal duty time is considered to be voluntary overtime for which overtime pay or compensatory time in accordance with the Fair Labor Standards Act is mandated. An employee's participation is considered to be within the scope of employment, and additional compensation for participation is not allowed.[37]

C. Private Citizens: "[p]rivate citizens who are not enrolled in the DEERS may not be used in CIs conducted with Major Defense Program 8 funds...." (Appendix E, AR 40-38) Clinical research in MTFs is generally funded by Program 8 funds; research in U.S. Army Medical Research and Materials Command is funded with Major Defense Program 6 funds. AR 70-25 discusses the use of Program 6 funds for the use of contractor employees in research.

D. Retirees, and Dependents of Active Duty and Retired Military Personnel: may participate and be compensated on a fee basis, but a retiree in a study lasting longer than 30 days may have retired pay recomputed. Government policy further prohibits acceptance of voluntary services from private citizens that could result in a future claim against the United States for the value of the services.

E. Minors and Other Persons Incapable of Giving Consent: minors and persons incapable of giving consent (mentally incompetent adults, such as one suffering from dementia) may not be used as study subjects in the Department of Defense unless the study intends to benefit each participant.[38] It is not necessary that the intended benefit actually occur, however.

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[36] 24 U.S.C. § 30; AR 40-38, paragraph 3-6*b*(9).
[37] AR 40-38, paragraph 3-6*b*(14).
[38] 10 U.S.C. § 980; AR 40-38, paragraph 3-3*a.*

1. Any study involving a control group (a group of subjects not receiving the research treatment for comparison purposes) could only use individuals in this class in the control group if there was an intent to benefit study subjects *in both the treatment and control groups*. If there is no intent to benefit the control group, participation in the research is not intended to, and in fact does not, benefit the control group.

2. Additionally, for minors, the risk must justify the intended benefit, the intended benefits must be at least as favorable as available alternatives, and the minor, if capable, has assented to participation in the study. Consent, of course, must be obtained in advance of participation from a legally authorized representative, usually, but not always, a parent.[39]

10. Funding of Clinical Investigation.[40]

A. Clinical investigation programs may be funded with Major Defense Program 8 funds, with Major Defense Program 6 funds (as determined by the Commander, USAMRMC), or by grants from other Federal agencies.

B. Grants may also be obtained from tax-exempt private sources (foundations, funds or educational institutions) operated primarily for scientific or educational purposes.

C. Cooperative Research and Development Agreements (CRDAs) establish a joint research efforts between Federal and non-Federal parties, and may provide for the transfer of funds, and the provision of personnel, services, facilities, equipment or other resources from the non-Federal party for the support of specified research.[41] The CRDA is the preferred method of obtaining non-federal support for research. Master agreements have been entered into with the Henry M. Jackson Foundation, United Services Clinical Research, Inc., and T.R.U.E. Research Foundation by CIRO.

D. Gifts in support of clinical investigation programs must be processed under the provisions of AR 1-100, and MEDCOM Supplement 1 to AR 1-100. All gifts, regardless of value, may be accepted only after approval in accordance with AR 1-100. However, drugs, placebos, biologics and medical devices that are not commercially available are not considered gifts and may be accepted and accounted for in accordance with local directives.[42]

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[39]AR 40-38, paragraph 3-3*m.*
[40]AR 40-38, paragraph 3-6.
[41]AR 70-57.
[42]DoD Directive 6000.8, paragraph E.3.a; AR 40-38, paragraph 3-6*b*(3)*(g)*. See footnote 11 on treatment of loaned equipment.

11. Scientific Integrity and Biomedical Research.

Any institution receiving Public Health Service (PHS) funding is required to establish an administrative process for reviewing, investigating and reporting allegations of scientific misconduct in connection with PHS-sponsored research at the institution, and to comply with its own administrative process and the requirements of the PHS rule found at 42 *Code of Federal Regulations* § 50. Similarly, the National Science Foundation (NSF) requires the establishment of such a procedure for entities receiving funding. The National Science Foundation rule may be found at 45 *Code of Federal Regulations* § 689. Establishment of a written is required for any Army medical facility receiving funds (research grants, for example) from either PHS or NSF.

12. Warning, Changes Pending!

This is, as might be expected, a fast developing area. Revisions are being made to the basic DOD directives and other source references at the time of the publications of this article.

REFERENCES.

1. Federal Statutes:

A. 10 U.S.C. 980.

B. 24 U.S.C. 30.

2. *Code of Federal Regulations:*

A. 32 *CFR* § 219 (Controlling implementation of the "Federal Common Rule" on human subjects research).

B. 45 *CFR* § 46.

C. 42 *CFR* § 50.

3. Department of Defense Directives:

A. DoD Directive 6000.8, *Funding and Administrative of Clinical Investigation Programs*, December 6, 1985.

B. DoD Directive 3216.2, *Protection of Human Subjects in DoD-Supported Research*, January 7, 1983.

4. Army Regulations:

A. AR 1-100, with MEDCOM Supplement 1 to AR 1-100, *Gifts and Donations*, 15 November 1983, and 8 October 1997.

B. AR 40-3, *Medical, Dental, and Veterinary Care*, 15 February 1985.

C. AR 40-7, *Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances*, 4 January 1991.

D. AR 40-38, *Clinical Investigation Program*, 1 September 1989.

E. AR 70-18, with HSC Supplement 1, *The Use of Animal in DOD Programs*, 1 August 1984, and 10 April 1985.

F. AR 70-25, *Use of Volunteers as Subjects of Research*, 25 January 1990 (applicable to USAMRMC funded research).

G. AR 70-57, *Military-Civilian Technology Transfer*, 25 July 1991.

H. HSC Regulation 40-23, with Changes 1 and 2, *Management of Clinical Investigations Protocols and Reports*, 14 October 1981.

5. MEDCOM Clinical Investigation Site:

http://kmn.army.mil/auth/hckb/ci.html.